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[Intervention Review]

Heliox for croup in children

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ABSTRACT

Background

Croup is thought to be triggered by a viral infection and is characterised by respiratory distress due to upper airway inflammation and swelling of the subglottic mucosa in children. Mostly it is mild and transient and resolves with supportive care. In moderate to severe cases, treatment with corticosteroids and nebulised epinephrine (adrenaline) is required. Corticosteroids improve symptoms but it takes time for a full effect to be achieved. In the interim, the child is at risk of further deterioration. This may rarely result in respiratory failure necessitating emergency intubation and ventilation. Nebulised epinephrine may result in dose-related adverse effects including tachycardia, arrhythmias and hypertension and its benefit may be short-lived. Helium-oxygen (heliox) inhalation has shown therapeutic benefit in initial treatment of acute respiratory syncytial virus (RSV) bronchiolitis and may prevent morbidity and mortality in ventilated neonates. Heliox has been used during emergency transport of children with severe croup and anecdotal evidence suggests that heliox relieves respiratory distress.

Objectives

To examine the effect of heliox on relieving symptoms and signs of croup, as determined by a croup score (a tool for measuring the severity of croup).

To examine the effect of croup on rates of admission or intubation (or both), through comparisons of heliox with placebo or any active intervention(s) in children with croup.

Search methods

We searched CENTRAL 2013, Issue 10, MEDLINE (1950 to October week 5, 2013), EMBASE (1974 to November 2013), CINAHL (1982 to November 2013), Web of Science (1955 to November 2013) and LILACS (1982 to November 2013). In addition, we searched two clinical trials registries: the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) and clinicaltrials.gov (searched 12 November 2013).

Selection criteria

Randomised controlled trials (RCTs) and quasi-RCTs comparing the effect of helium-oxygen mixtures with placebo or any active intervention(s) in children with croup.

Data collection and analysis

Two review authors independently identified and assessed citations for inclusion. A third review author resolved disagreements. We assessed included trials for allocation concealment, blinding of intervention, completeness of outcome data, selective outcome reporting and other potential sources of bias. We reported mean differences for continuous data and odds ratios for dichotomous data. We descriptively reported data not suitable for statistical analysis.

Main results

We included three RCTs with a total of 91 participants. One study compared heliox 70%/30% with 30% humidified oxygen administered for 20 minutes in children with mild croup and found no statistically significant differences in the overall change in croup scores between heliox and the comparator. In another study, children with moderate to severe croup were administered intramuscular dexamethasone 0.6 mg/kg and either heliox 70%/30% with one to two doses of nebulised saline, or 100% oxygen with one to two doses of nebulised racaemic epinephrine for three hours. In this study, the heliox group's croup scores improved significantly more at all time points from 90 minutes onwards. However, overall there were no significant differences in croup scores between the groups after four hours using repeated measures analysis. In a third study, children with moderate croup all received one dose of oral dexamethasone 0.3 mg/kg with heliox 70%/30% for 60 minutes in the intervention group and no treatment in the comparator. There was a statistically significant difference in croup scores at 60 minutes in favour of heliox but no significant difference after 120 minutes. It was not possible to pool outcomes because the included studies compared different interventions and reported different outcomes. No adverse events were reported.

Authors' conclusions

There is some evidence to suggest a short-term benefit of heliox inhalation in children with moderate to severe croup who have been administered oral or intramuscular dexamethasone. In one study, the benefit appeared to be similar to a combination of 100% oxygen with nebulised epinephrine. In another study there was a slight change in croup scores between heliox and controls, with unclear clinical significance. In another study in mild croup, the benefit of humidified heliox was equivalent to that of 30% humidified oxygen, suggesting that heliox is not indicated in this group of patients provided that 30% oxygen is available. Adequately powered RCTs comparing heliox with standard treatments are needed to further assess the role of heliox in children with moderate to severe croup.

PLAIN LANGUAGE SUMMARY

Helium-oxygen (heliox) treatment for croup in children

Croup is an acute illness commonly seen in children up to six years of age but mostly by the age of two. It is triggered by viral infections causing upper airway obstruction with varying degrees of respiratory distress. Mostly, it is mild and transient and resolves with supportive care. Croup is characterised by a barking cough, hoarseness, varying degrees of inspiratory stridor (abnormal breathing sound) and chest wall retractions and is usually preceded by one to three days of upper respiratory tract infection symptoms. The peak croup seasons are autumn and winter but can occur at any time.

Corticosteroids are an accepted treatment for moderate to severe croup, supplemented in more severe cases by nebulised epinephrine and oxygen. Epinephrine is often effective and safe but can have undesired effects (such as increased heart rate and anxiety). Corticosteroids improve croup symptoms but it takes time for their full effect to be achieved. In the meantime the child remains at risk of deterioration. This may rarely result in the development of respiratory failure, which may require emergency intubation and ventilation. Therefore, finding a safe and effective treatment to bridge the gap between the administration and effectiveness of the corticosteroids is important for clinical practice.

Some studies have shown a benefit of using heliox in children with croup. Heliox, a gas with lower density than air or oxygen, is believed to reduce the resistance to gas flow in narrowed upper airways, potentially improving symptoms and signs of respiratory distress. This review found three randomised controlled trials (RCTs) assessing the effect of heliox in 91 children with croup. Heliox did not appear to be more effective than administration of 30% oxygen in children with mild croup. In children with moderate to severe croup who had been administered oral or intramuscular corticosteroids, heliox appeared to be at least as effective as continuous 100% oxygen with one to two doses of nebulised racaemic epinephrine (adrenaline as a fine spray) in one study. It was slightly more effective than no treatment in another study. There were no adverse effects or outcomes reported. The included trials were small and had a number of methodological limitations. Further methodologically well-designed RCTs with more participants are needed to further assess the role of heliox in managing children with moderate to severe croup. The evidence is current to November 2013.

BACKGROUND

Description of the condition

Croup (also know as viral laryngotracheobronchitis), is a common respiratory syndrome in children, which may progress to an acute respiratory obstruction. It is characterised by a barking cough, hoarseness, varying degrees of inspiratory stridor and chest wall retractions. It is usually preceded by a one to three-day period of viral upper respiratory tract infection symptoms. Croup commonly affects children up to the age of six years, with the highest incidence in the second year of life (Denny 1983; Rittichier 2000). A seasonal variation in the occurrence of croup, with a peak in the autumn and winter, has been reported (Denny 1983; Segal 2005). Two commonly used methods for assessing the severity of croup are the Westley and Taussig Croup Scales (Taussig 1975; Westley 1978). The croup score is assigned based on the following observed parameters: level of consciousness, stridor, colour, air entry and retractions. The Westley croup score has numerical values ranging from zero to 17. Values less than four correspond to mild croup, four to six to moderate croup and more than six to severe croup. The Taussig scale also has numerical values ranging from zero to 15. A score of less than four corresponds to mild croup, four to seven corresponds to moderate croup and more than seven corresponds to severe croup (Taussig 1975; Westley 1978).

Croup is thought to be triggered by a viral infection, most commonly by human parainfluenza virus (HPIV), particularly HPIV type 1 and less commonly by influenza virus, respiratory syncytial virus (RSV), rhinovirus, adenovirus, enteroviruses and *Mycoplasma pneumoniae* (*M. pneumoniae*) (Denny 1983; Marx 1997; Segal 2005). Viral invasion of the subglottic mucosa causes inflammation and oedema, leading to narrowing of the upper airway. As this narrowing progresses, the pressure gradient necessary to move air through the upper airway becomes greater, leading to an increased effort in breathing. This may result in fatigue of the respiratory muscles and subsequently lead to respiratory failure, requiring emergency intubation. Systemic, oral or nebulised corticosteroids are the currently accepted treatment for moderate to severe croup, supplemented in more severe cases by nebulised epinephrine (Bjornson 2011) and oxygen. Antibiotics do not play a role in the treatment of acute croup. Corticosteroids have been shown to improve symptoms of croup but it takes time for their full effect to be achieved (Russell 2012). Nebulised budesonide has been shown to have a beneficial effect as early as two hours after administration (Fitzgerald 1996; Klassen 1998) but in the meantime the child remains at risk of deterioration and of developing respiratory failure, requiring emergency intubation and ventilation.

Description of the intervention

Helium is a biologically inert, colourless, odourless and non-combustible gas and was first discovered in 1868 by Jannsen and Lockyer. In the early 1930s Barach pioneered the successful use of a helium-oxygen mixture (heliox) in the treatment of adults and children with asthma and upper airway obstruction (Barach 1935; Barach 1936). However, it was not until the 1980s that helium-oxygen mixtures regained popularity, possibly due to the rising mortality from asthma (Robin 1988). This led to an increase in clinical trials assessing the effect of heliox in the management of acute upper and lower airway obstructive disorders in children (Cambonie 2006; Grozs 2001; Hollman 1998; Martinon-Torres 2002). Heliox is used in concentrations of helium/oxygen of 80%/20%, 60%/40% or 70%/30%.

How the intervention might work

Heliox has a similar viscosity and a substantial sevenfold lower density than air and when combined with oxygen results in heliox, a gas mixture with an up to threefold (heliox 80/20) lower density than air (Papamoschou 1995). The density of a gas mixture is proportional to the Reynolds number (Re), a dimensionless ratio of the inertial to the viscous force and will thus have an effect on the type of gas flow present in the airway. It is known that turbulent flow occurs when Re > 3000 and laminar flow occurs when Re < 2000 (Glauser 1969). Pathological narrowing of the airway, as seen in croup, will lead to increased turbulence and higher gas flow resistance, resulting in an increased breathing effort. In theory, a gas of low density, such as heliox, should create a less turbulent or even laminar flow, by reducing the Reynolds number, leading to a decrease in resistance to gas flow and the work of breathing (Houck 1990). Heliox is also believed to improve gas exchange, due to a delivery of increased tidal volume as a result of lowering the resistive forces within the airway (Katz 2001; Katz 2003). A Cochrane Review investigating the role of heliox inhalation therapy in infants with RSV bronchiolitis concludes that the addition of heliox therapy to standard medical care may significantly reduce a clinical score evaluating respiratory distress in the first hour after starting treatment (Liet 2010). Similarly, a Cochrane Review in children with asthma suggests that heliox might have beneficial effects in patients (children or adults) with severe obstruction (Rodrigo 2010).

Why it is important to do this review

Croup can cause anxiety and distress to affected children and their parents. In mild cases, supportive treatment may suffice but in moderate to severe cases, more aggressive therapy may be required to prevent exhaustion and respiratory failure. The available treatment options for croup are limited. Corticosteroids take time for their clinical effects to be achieved. Nebulised epinephrine (adrenaline) is widely used. It has a rapid onset and short-lived

benefit but can be associated with dose-related side effects such as tachycardia, hypertension and arrhythmias. Treatment of croup with heliox has demonstrated a beneficial effect, albeit in a small numbers of patients (Beckmann 2000; DiCecco 2004; Duncan 1979; Nelson 1982; Smith 1999) and in one study the benefit appeared to be no different to nebulised epinephrine (Weber 2001). No significant evidence of benefit was reported in the previous version of this review (Vorwerk 2010), but there are new data from a Spanish randomised controlled trial (RCT) to suggest that heliox, when added to corticosteroids, clinically improves moderate croup (Pardillo 2009). Also a recently published retrospective cohort study indicates that heliox, when added to standard treatment for transporting critically ill children with croup, provides rapid and sustained improvement in croup scores with no extension of length of stay in the intensive care unit (ICU) (Kline-Krammes 2012). There is a need for an updated review of the evidence regarding the role of heliox in children with croup to guide clinical practice.

OBJECTIVES

To examine the effect of heliox on relieving symptoms and signs of croup, as determined by a croup score (a tool for measuring the severity of croup).

To examine the effect of croup on rates of admission or intubation (or both), through comparisons of heliox with placebo or any active intervention(s) in children with croup.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and quasi-RCTs comparing the effect of helium-oxygen mixtures with placebo or any active intervention(s).

Types of participants

Children with the clinical diagnosis of croup or laryngotracheobronchitis. We excluded other upper airway obstruction conditions such as epiglottitis, foreign body inhalation or peritonsillar abscess.

Types of interventions

We included studies where the effect of heliox was compared to placebo or any active intervention(s); and where similar routes of administration were used for both groups.

Types of outcome measures

Primary outcomes

1. Change in croup score.

Secondary outcomes

1. Change in respiratory rate.
2. Change in oxygen requirements.
3. Change in heart rate.
4. Rate and duration of hospitalisation.
5. Rate and duration of intubation.
6. Rate and duration of admission to paediatric intensive care units.
7. Rate of return to medical care for ongoing croup symptoms.
8. Parental anxiety.
9. Adverse events.
10. Other reported outcomes.

Search methods for identification of studies

Electronic searches

We conducted an updated search in the Cochrane Central Register of Controlled Trials (CENTRAL) 2013, Issue 10, part of *The Cochrane Library*, www.thecochranelibrary.com (accessed 12 November 2013), which contains the Acute Respiratory Infections (ARI) Group's Specialised Register, MEDLINE (January 2009 to October week 5, 2013), EMBASE (May 2009 to November 2013), Web of Science (1955 to November 2013) and LILACS (1982 to November 2013). Details of the previous search are in Appendix 1.

MEDLINE and CENTRAL were searched using the following terms. The search terms were adapted for EMBASE (Appendix 2), CINAHL (Appendix 3), Web of Science (Appendix 4) and LILACS (Appendix 5).

MEDLINE (Ovid)

1 Croup/
2 croup.tw.
3 laryngotracheit*.tw.
4 laryngotracheo*.tw.
5 laryngo tracheo bronchit*.tw.

6 Parainfluenza Virus 2, Human/ or parainfluenza virus 1, human/ or parainfluenza virus 3, human/
7 parainfluenza*.tw.
8 or/1-7
9 Helium/
10 helium*.tw,nm.
11 heliox.tw,nm.
12 (heo2 or he-o2 or he o2).tw,nm.
13 or/9-12
14 8 and 13
There were no language or publication restrictions.

Searching other resources

We searched two international clinical trials registries (last searched 12 November 2013): the World Health Organization International Clinical Trials registry Platform (WHO ICTRP) and clinicaltrials.gov for any ongoing or unpublished trials. We also searched the references of review articles and all reports reviewed in full text to find other potentially eligible studies. We contacted the trial authors of the included studies and a leading medical gas supplier, British Oxygen Company (BOC), to enquire whether they knew of any further published or unpublished trials.

Data collection and analysis

Selection of studies

Two review authors (IM and NS) independently assessed the titles and abstracts of all citations to identify potentially relevant reports. All review authors agreed on a list of reports which were reviewed in full, to determine whether they fulfilled the inclusion criteria. Agreement about trial inclusion was reached by consensus.

Data extraction and management

The review authors independently extracted data on:

1. design (description of randomisation, use of blinding, allocation concealment, handling of study withdrawals);
2. participants (total number, setting, age, exclusions);
3. intervention (type of helium-oxygen mixture, route of intervention, control group intervention, study duration); and
4. outcomes (primary, secondary, outcome analysis).

We used a standard data extraction form and we reached agreement by consensus.

Assessment of risk of bias in included studies

The review authors assessed the risk of bias in the included studies by using The Cochrane Collaboration's 'Risk of bias' tool, addressing the following domains (Higgins 2011).

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel; blinding of outcome assessment.
4. Incomplete outcome data.
5. Selective reporting.
6. Other sources of bias.

Unit of analysis issues

We analyzed the outcomes of individual patients. In studies where the unit of analysis (individual patients) was not the same as the unit of randomisation, such as is the case in cluster-randomised trials or cross-over trials, we planned to use the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) to adjust for the effect of clustering. In case of repeated measures over time (such as measurement of croup scores at different time points after receiving the intervention) we planned to select a single time point and meta-analyse only data at this time for studies in which it was presented (Higgins 2011). We planned to select a short-term time point as this is clinically relevant for studies comparing heliox and other treatments for children with croup.

Dealing with missing data

We contacted the authors of the included studies to obtain missing data.

Assessment of heterogeneity

We assessed the included studies for clinical and methodological heterogeneity. We planned to assess statistical heterogeneity by calculating the P value of the Chi^2 test and the I^2 statistic with an I^2 statistic of 50% or more considered as significant heterogeneity.

Data synthesis

We presented continuous outcomes, such as change in croup score, as mean difference (MD) with 95% confidence interval (CI). In case pooled studies reported a different croup score at the same time points, we planned to combine the outcomes by using the standardised mean difference (SMD) with 95% confidence interval (CI). We planned to use the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) to calculate the SMD.

If standard deviations or confidence intervals (required for calculating the SMD) were not available from the study reports we used methods as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) to impute the missing standard deviations from the standard error of the mean by multiplying by the square root of the sample size or from CIs from the mean, whichever one was provided in the report.

We presented dichotomous variables, such as proportion of hospital admissions, as odds ratio (OR) with 95% CI. We reported all identified adverse events.

We planned to pool data using both fixed-effect and random-effects models as described in the *Cochrane Handbook for Systematic Reviews of Interventions* and to explore the impact of each on the overall treatment effect estimate (Higgins 2011).

Sensitivity analysis

We planned to investigate the impact of heterogeneity on the overall estimated effect of the intervention.

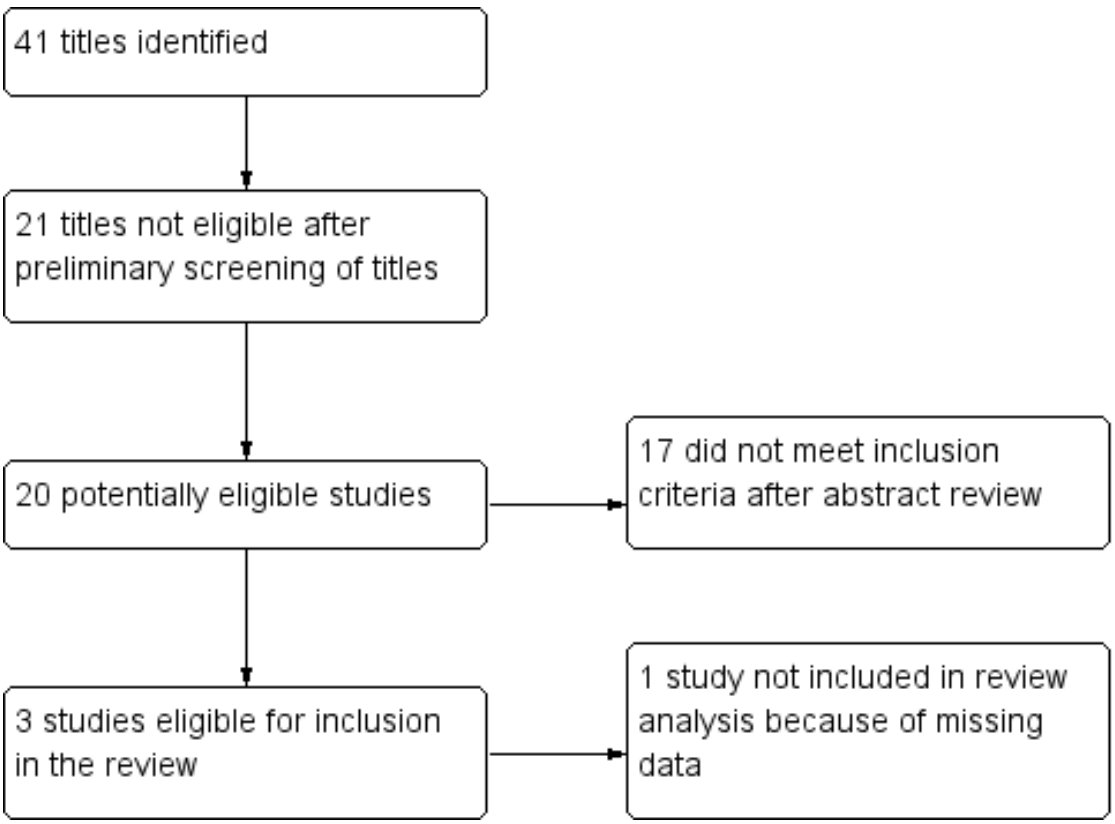
RESULTS

Description of studies

Results of the search

An updated search was conducted in November 2013 and identified 41 trial reports. Twenty-one titles were excluded after preliminary screening; 20 were considered potentially eligible. After abstract review, 17 studies did not meet the inclusion criteria and were excluded. Three studies met the inclusion criteria (Figure 1). The previous search conducted in June 2009 identified 45 trial reports with two studies meeting the inclusion criteria.

Figure 1. Flow diagram of study selection



Included studies

We identified three studies (with a total of 91 participants) suitable for inclusion in this review. Two studies were published in English and one in Spanish. All trials included in the review are randomised controlled trials and the study participants have sim-

ilar characteristics in terms of age and sex distribution. The characteristics of included studies are described in the Characteristics of included studies table and summarised in Table 1.

The trial by Terregino 1998 enrolled children with *mild croup* aged between six months and four years, presenting to the Emergency Department. It was a small study with 15 participants; eight received heliox and seven received 30% oxygen, both delivered via humidification. Children were excluded from entering the study if they had a presumed diagnosis of epiglottitis, a history of chronic upper airway obstruction, if they were in severe respiratory distress or their oxygen requirements exceeded 2 L/min to maintain an oxygen saturation of at least 95%. The treatments were delivered via a tight-fitting mask for a 20-minute period. No additional treatments were given to the study participants. The main outcome of the study was a change in Westley croup score (Westley 1978) at 20 minutes. Other outcomes were measured at five-minute intervals for 20 minutes and they included heart rate, respiratory rate and oxygen saturation. The difference in the mean baseline croup scores between the intervention and comparator groups was not significant. No adverse events were reported during the study period and all patients were discharged from the Emergency Department.

In the study by Weber 2001, 29 children aged between six months and three years with a diagnosis of *moderate to severe croup*, defined as a modified Taussig 1975 croup score $\geq$ five or a score of three in any of the five categories, were enrolled from the Emergency Department. All children received continuous cool mist and 0.6 mg/kg of intramuscular dexamethasone. Fourteen children were then randomised to receive heliox and 15 children were randomised to receive 100% oxygen plus one to two doses of nebulised racaemic epinephrine. Gas therapy was administered via a facemask or tent house continuously for three hours followed by a further 60-minute observation period. The primary outcome measure was the change in croup score over time (at 30, 60, 90, 120, 150, 180 and 240 minutes) and the secondary outcomes were changes in oxygen saturation, respiratory rate and heart rate. There was no significant difference in the mean baseline croup score between the intervention and comparator group. No adverse events were reported during the study.

Pardillo 2009 enrolled 47 children aged between 6 and 36 months with *moderate croup* (defined as a Taussig score between five and eight). A single dose of 0.3 mg/kg of dexamethasone was administered orally to all study participants. Heliox was administered to 24 children via a mask with a reservoir to prevent re-inhalation for a period of one hour and 23 children received no treatment unless their oxygen saturations fell to below 92% during the study, in which case oxygen was administered by nasal prongs. Children were excluded if they had congenital or acquired cardiac conditions, bronchopulmonary dysplasia, stenosis or malformations of the trachea, bronchospasm at diagnosis, intolerance of oral dexamethasone or if they had been treated with corticosteroids in the previous two weeks. The main outcome measures were changes in the Taussig croup score and respiratory rate, which were analyzed at 60 and 120 minutes. The other outcome measures included were: need for nebulised rescue epinephrine, admission rate and re-consultation within the following 72 hours. There was no significant difference in the mean baseline croup score or respiratory rate between the intervention and control group. No adverse events were reported during the study.

Excluded studies

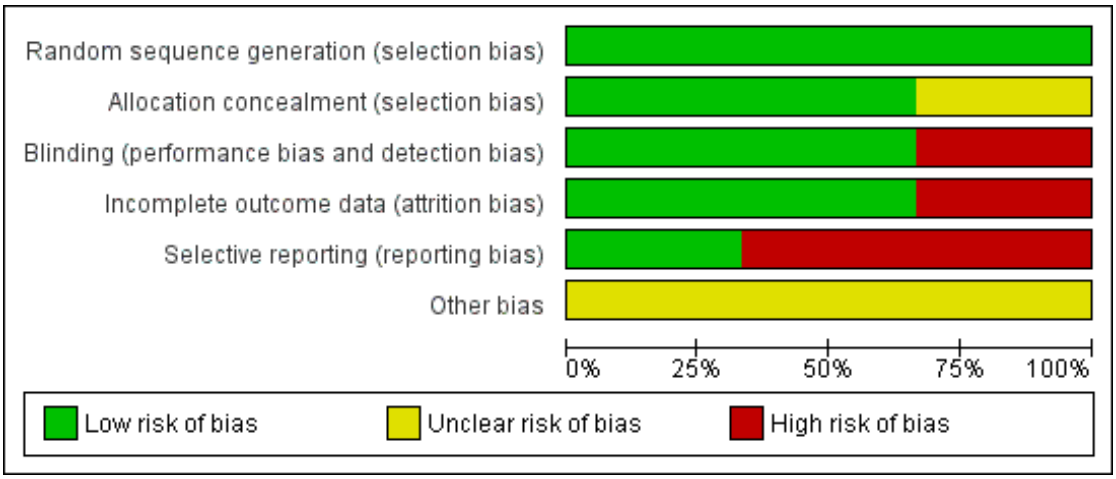
The previous search in 2009 excluded 43 reports of which 10 were considered potentially relevant but excluded after a full-text review (Characteristics of excluded studies table). Two were case series of children with post-intubation or refractory viral croup (Duncan 1979; Nelson 1982). Smith 1999, Beckmann 2000 and DiCecco 2004 reported cases of helium-oxygen treatment in croup. Iglesias 2007 conducted a prospective, uncontrolled cohort study including croup and other airway obstruction. The other excluded papers were non-systematic reviews addressing different aspects of croup management (Gupta 2005; Johnson 2009; Myers 2004; Myers 2006).

We conducted an updated search in March 2013 and excluded 38 reports. Three records were also excluded in the 2009 review (Beckmann 2000; Duncan 1979; Myers 2006). Of the 17 new records identified in the 2013 search seven were excluded after a preliminary title review. Ten studies assessed after retrieving the full text were subsequently excluded; five were not RCTs and five were literature reviews (Brown 2002; Choi 2012; Frazier 2010; Kaditis 1998; Kline-Krammes 2012; Nicolai 2012; Pitluk 2011; Rosekrans 1998; Wald 2010; Wright 2005) (see Characteristics of excluded studies).

Risk of bias in included studies

The methodological quality of all included studies as judged by the review authors is illustrated in Figure 2 and in the Risk of bias in included studies tables.

Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.



Allocation

Allocation was adequately concealed in two of the three trials. Terregino 1998 used sequentially numbered, sealed envelopes and Weber 2001 used computer randomised allocation. Pardillo 2009 did not describe how concealment was carried out despite using a computer program for randomisation.

Blinding

The trials by Terregino 1998 and Weber 2001 are considered to have a low risk of bias as the participants and outcome assessors were blinded; only the respiratory therapists were not blind to treatment allocation. The trial by Pardillo 2009 is considered to have a high risk of performance and detection bias because neither the participants nor the assessors were blinded to treatment.

Incomplete outcome data

There was no evidence of missing outcome data in the Terregino 1998 study and no study participants were lost to follow-up. The trial by Weber 2001 is categorised as high risk of bias because there is insufficient explanation of why some participants were excluded from the study and also no raw data for the main outcomes of the study were provided. There was no evidence of missing outcome data in the Pardillo 2009 study and therefore it is categorised as having a low risk of attrition bias even though there is no explanation as to why some excluded participants did not meet the study inclusion criteria.

Selective reporting

Terregino 1998 reported all of the expected study outcomes (low risk of reporting bias). The study by Weber 2001 did not present expected study outcomes at any of the time points. Pardillo 2009 reported expected major outcome data but failed to report if any participants required supplementary oxygen.

Other potential sources of bias

The study by Terregino 1998 used a convenience sample which carries a potential risk of bias. There may also be further potential risk of bias in the trial by Weber 2001 because of the lack of outcome data. None of the studies disclosed any funding sources and/or potential conflicts of interest.

Effects of interventions

Primary outcome

Change in croup score

The effect of heliox on symptoms and signs of croup, presented as change in croup score between pre- and post-intervention was reported in all three included studies. The croup scores were measured at different time points after the interventions: at 20 minutes in Terregino 1998, at 30, 60, 90, 120, 150, 180 and 240 minutes in Weber 2001 and at 60 and 120 minutes in Pardillo 2009. In the Terregino 1998 study the mean *change* in croup scores after 20 minutes of treatment favoured the intervention group (mean

difference (MD) of change 0.83, 95% confidence interval (CI) 95% -0.7 to 2.36) (Analysis 1.1). The Weber 2001 study did not present any raw croup scores (except in graphical form) at the measured time points. In the Pardillo 2009 study the mean difference (MD) in croup scores measured in both groups at 60 minutes was statistically significant and in favour of the heliox group: MD -1.12 (95% CI -2.06 to -0.18) (Analysis 2.2) and at 120 minutes was not statistically significant with MD -0.71 (95% CI -1.72 to 0.30) (Analysis 2.3).

The Pardillo 2009 study compared changes in croup scores in children with moderate croup (Taussig scale five to six) and those with severe croup (Taussig scale seven to eight) and found a more significant improvement in those with severe croup.

We only used data that were available from the publications, as no additional data were obtained from the authors of the included studies.

Secondary outcomes

Only data from Terregino 1998 and Pardillo 2009 were available for analysis.

1. Change in respiratory rate

In the Terregino 1998 study the MD in change of respiratory rate between pre- and post-intervention at 20 minutes was 6.4 (95% CI -1.38 to 14.18) (Analysis 1.4). In the Pardillo 2009 study the respiratory rate was more reduced in the heliox group than in the control group both at 60 and at 120 minutes. The MD in change of respiratory rate between pre- and post-intervention at 60 and 120 minutes was -4.94 (95% CI -9.66 to -0.22) (Analysis 2.4) and -3.17 (95% CI -7.83 to 1.49) (Analysis 2.5), respectively. There were no statistically significant differences between treatment groups in respiratory rate (P = 0.94) in the Weber 2001 study (no absolute numbers reported).

2. Change in oxygen requirements

The need for oxygen was not reported in any of the three included trials. However, oxygen saturation of the included children was reported in Terregino 1998 and Weber 2001. Terregino 1998 reports that the mean oxygen saturation was stable over time in the two groups. There were no statistically significant differences between treatment groups in arterial oxygen saturation (P = 0.28) in the Weber 2001 study (no absolute numbers reported).

3. Change in heart rate

In the Terregino 1998 study, the MD in change of heart rate pre- and post-intervention at 20 minutes was 14.5 (95% CI -8.49 to 37.49) (Analysis 1.3), favouring heliox. There were no statistically significant differences between treatment groups in heart rate (P = 0.29) in the Weber 2001 study (no absolute numbers reported). In the Pardillo 2009 study, this outcome was not reported.

4. Rate and duration of hospital admission

In the Terregino 1998 study, all patients were discharged from the emergency department. In the Pardillo 2009 study two patients in the control group and one in the treatment group were hospitalised (P = 0.609) and the odds ratio (OR) for the proportion of patients who were admitted was 0.46 (95% CI 0.04 to 5.41) (Analysis 2.6). The OR favoured heliox. This outcome is not reported in the Weber 2001 study.

5. Rate and duration of intubation

None of the study participants in the three included studies were reported as requiring intubation.

6. Rate and duration of admission to paediatric intensive care units

In the Pardillo 2009 study two patients in the heliox group (8.3%) and two in the control group (8.7%) re-presented at the emergency department within 72 hours of first presentation (P = 1) (Analysis 2.6). The Terregino 1998 and Weber 2001 studies do not report this outcome.

7. Rate of return to medical care for ongoing croup symptoms

The Terregino 1998 study did not report whether there were any patients who re-presented to the hospital. In the Pardillo 2009 study the OR for the proportion of patients who re-presented to hospital in the 72 hours following the intervention was 0.95 (95% CI 0.12 to 7.41) (Analysis 2.7) and The OR favoured heliox.

8. Parental anxiety

This outcome was not reported in the three included studies.

9. Adverse events

There were no reported adverse events in any of the three included trials. Terregino 1998 mentions there was “no recorded complication”.

10. Other reported outcomes

Terregino 1998 reports that none of the participating children required administration of racaemic epinephrine.The Weber 2001 study reports that “four patients in the epinephrine arm and three in the Heliox arm received a second dose of racaemic epinephrine and saline placebo, respectively. Outcomes for both groups were

similar". In the Pardillo 2009 study the OR for the proportion of participants who required rescue adrenaline was 0.16 (95% CI 0.02 to 1.46) (Analysis 2.1). The other studies did not report data contributing to this outcome. The OR favoured heliox.

DISCUSSION

Summary of main results

Only three RCTs with a total of 91 participants (Terregino 1998; Weber 2001; Pardillo 2009) assessed the effect of heliox inhalation as treatment in children with a diagnosis of croup. Terregino 1998 compared helium-oxygen (70/30) inhalation with humidified oxygen (30%). Weber 2001 compared helium-oxygen (70/30) inhalation with oxygen (100%) and nebulised racaemic epinephrine and Pardillo 2009 compared heliox 70/30 with no treatment. Overall, in all studies there was more improvement in the croup scores from pre- to post-intervention with heliox than with the comparator intervention, although it did not reach statistical significance in two of the studies. There were no significant changes in heart rate, respiratory rates or oxygen saturation between the intervention and comparison groups. There were no adverse events and there was no need for intubation reported in any of the study participants. Some patients were admitted to hospital and some re-presented at the Emergency Department in the Pardillo 2009 study. The study by Weber 2001 lacked data on the main outcomes and we were unable to obtain data after contacting the authors. Therefore, it is difficult to interpret the findings of this study.

Overall completeness and applicability of evidence

In the case series described by Duncan 1979, seven children (aged from newborn to three years) with severe airway obstruction due to post-intubation or infectious croup were given heliox as a carrier for oxygen. Even though most of the children had underlying medical problems, helium-oxygen inhalation was found to significantly reduce respiratory distress as measured by croup score and it prevented the need for tracheal intubation. Nelson 1982 described a further case series of 14 children (aged from three to 21 months) with viral croup who were referred for possible tracheal intubation or tracheostomy. These children were commenced on helium-oxygen inhalation and subsequently an improvement in respiratory distress was observed, while none of the participants required intubation. Both case series included a heterogenous study population and lacked a control group, which makes it very difficult to comment on the contribution of heliox mixtures to the observed clinical outcomes. Anecdotal evidence of benefit from heliox is further supported by Smith 1999 who reported dramatic relief of respiratory distress in three children with croup who were commenced on heliox therapy. A recently published retrospective chart review by Kline-Krammes 2012 included 35 children, 17 treated with heliox and 18 controls transported by air and admitted to paediatric intensive care. Those treated with heliox had a higher baseline croup score compared to the controls. The improvement in croup scores in the heliox group was more rapid and there was no difference in the number of children requiring nebulised racaemic epinephrine during transport. The length of stay in the paediatric intensive care unit (PICU) and hospital was similar between the two groups.

Data from the included studies do not allow for a robust conclusion as to whether heliox is an effective treatment for relieving symptoms and signs of croup in children or on rates of admission or intubation in these children. All the studies reported changes in croup scores while other review outcomes were not consistently reported. We found only three trials with a total of 91 participants that met the inclusion criteria for our review.

The first RCT to assess the effect of heliox in children with croup was Terregino 1998. This study showed that there was no statistical significance in the mean change of croup scores pre- and post-intervention between the control and heliox group, suggesting that heliox was as effective but not more effective than humidified oxygen in reducing croup score. A limitation, however, is the exclusion of all children with severe croup who could have benefited from the intervention and the period of gas application was short compared to the other studies. Therefore, no conclusion can be drawn about the benefit of heliox in children with severe croup. None of the participants received corticosteroids or epinephrine, contrary to current standard practice in moderate to severe croup, making it difficult to apply the results to current clinical care.

The RCT by Weber 2001 found that overall heliox is as effective as, but not more effective than, nebulised racaemic epinephrine and 100% oxygen in improving croup scores. The study reported a statistically significant improvement in the intervention group after 90 minutes of treatment but in the absence of raw study data this is difficult to confirm. There are a number of limitations to this study. Participants requiring rescue nebulised epinephrine were excluded from the analysis, as were participants who did not tolerate the gas delivery system or had incomplete data. This may have led to a biased estimate of the treatment effect. Another limitation is the type of gas delivery system used to administer helium-oxygen, as entrainment of room air would have reduced the helium concentration of the inhaled gas mixtures and may have diminished any beneficial effects. Tent houses, as used in the study by Weber et al, are considered sub-optimal for heliox delivery as helium will accumulate at the top of the tent so the helium concentration reaching the upper airway of the patient will be markedly reduced (Martinon-Torres 2003; Stillwell 1989).

In the RCT by Pardillo 2009, heliox was compared with no treatment in children with moderate croup who had been administered corticosteroids. The study results show that treatment with heliox

provided a greater improvement in croup scores at 60 minutes and 120 minutes compared to baseline than no treatment. This study also reported other outcomes that are relevant for clinical practice. The number of participants requiring rescue adrenaline was higher in the control group (five patients) compared to the heliox group (one patient), as was the number of patients who were admitted (two in the control and one in the heliox group) but the number of patients who re-presented for treatment at 72 hours was similar (two patients in each group). This is the first RCT to report these findings and it also had more participants compared to the other two RCTs published. A limitation of the study was that it was open-label hence the investigators knew which arms the participants belonged to.

The duration of heliox administration varied in the three studies. The chosen duration of 20 minutes by Terregino 1998 might have been too short to demonstrate a significant benefit particularly because the studies by Pardillo 2009 and Weber 2001 reported a statistically significant difference in the improvement in the heliox group compared to the control group after 60 and 90 minutes of treatment respectively. Only the study by Pardillo 2009 reported data for some other outcomes that are relevant in clinical practice but unfortunately none of the studies fully addressed all the outcomes of the review.

The results of the studies indicate that heliox has a positive effect in reducing the severity of the signs and symptoms of croup as observed from the changes in croup scores and may be beneficial as part of initial treatment while waiting for the action of corticosteroids to take effect. Also there is evidence that heliox maybe useful during transport of children with severe croup.

Quality of the evidence

The quality of the evidence from the three included trials is variable. The trials by Terregino 1998 and Pardillo 2009 had a small sample size and it is likely that these studies were underpowered which may have resulted in a type II error and failure to find a true effect. The study by Weber 2001 presented incomplete outcome data which limits the quality of evidence available for interpretation. Another limitation of Pardillo 2009 was that it was an open-label study, resulting in a high risk of performance and detection bias.

Potential biases in the review process

To minimise any potential bias in the review process we have used a systematic and comprehensive search strategy. Two review authors independently identified and reviewed records and we feel confident that reasons for exclusion were consistent and appropriate. We have also contacted a leading medical gas supplier to enquire about any unpublished studies to minimise the risk of publication bias. Data analysis and extraction was carried out independently by two review authors and interpretation of the data and outcomes was thoroughly discussed by the whole author team. None of the authors has any potential conflict of interest in the outcome of this review.

Agreements and disagreements with other studies or reviews

This review is an update of a Cochrane Review (Vorwerk 2010) which had also been published elsewhere (Vorwerk 2008). One additional study was identified in our updated review which slightly changed the conclusion towards a potential benefit of heliox in the management of croup in young children. Given the paucity of evidence from randomised clinical trials, as more evidence becomes available this conclusion may be revised.

AUTHORS' CONCLUSIONS

Implications for practice

At present there is some evidence to suggest a short-term benefit of heliox inhalation in the treatment of moderate to severe croup in children who have been administered oral or intramuscular dexamethasone. In one study, the benefit appeared to be no different to that of the combination of 100% oxygen with one to two doses of nebulised racaemic epinephrine and in another study it appeared slightly more beneficial than no treatment. The difference in the croup score (Taussig score) between those administered heliox and those without additional treatment was around one point on the croup scale which was in the moderate range after 60 minutes. The clinical significance of this difference is not clear. In children with mild croup, the benefit of humidified heliox appeared to be equivalent to that of 30% humidified oxygen, suggesting that heliox is not indicated in this group of patients provided that 30% oxygen is available.

Implications for research

Adequately powered RCTs that compare heliox with standard treatments are needed to further assess the role of heliox therapy in the management of children with severe croup. These trials also need to incorporate clinical outcomes with health and economic relevance such as rate and duration of admission to paediatric intensive care units, rate and duration of intubation, rate of return to medical care for ongoing croup symptoms, rate and duration of hospital admission, parental anxiety and side effects.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by year of study]*

Terregino 1998

Methods	Randomised controlled trial
Participants	15 participants (8 intervention, 7 controls) who presented to the ED with features of croup, aged 6 months to 4 years. Excluded if severe respiratory distress, oxygen saturation < 95% on 2 L/min oxygen, or other causes of upper airway obstruction
Interventions	Intervention group: humidified helium-oxygen mixture (70%/30%) for 20 minutes Control group: humidified oxygen (30%) for 20 minutes
Outcomes	Primary: change in croup score at 20 minutes Secondary: change in heart rate, respiratory rate, oxygen saturation
Notes	No information on funding source or potential conflict of interest of the authors has been provided

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Use of sequentially, sealed envelopes available only to the respiratory therapist
Allocation concealment (selection bias)	Low risk	Allocation was adequately concealed
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence of missing outcome data
Selective reporting (reporting bias)	Low risk	All expected study outcomes were reported
Other bias	Unclear risk	Convenience sample used

Weber 2001

Methods	Randomised controlled trial
Participants	29 participants (14 intervention, 15 controls) who presented to the ED with features of moderate to severe croup (corresponding to a modified Taussig croup score $\geq$ 5), aged 6 months to 3 years. Excluded if known congenital cardiac or tracheo-broncho-pulmonary disease or if other causes of stridor

Weber 2001 (*Continued*)

Interventions	All patients received intramuscular dexamethasone 0.6 mg/kg Intervention group: helium-oxygen inhalation (70%/30%) and up to 2 doses of nebulised normal saline over 3 hours Control group: oxygen (100%) and up to 2 doses of nebulised racaemic epinephrine over 3 hours
Outcomes	Primary: change in croup score at 30, 60, 90,120, 150, 180, 240 minutes Secondary: change in heart rate, respiratory rate, oxygen saturation
Notes	"This study was funded, in part, by the Hurley Respiratory Therapy Department, Hurley Medical Center." No information on authors' conflict of interest provided

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Use of computer-generated randomisation scheme
Allocation concealment (selection bias)	Low risk	Allocation was adequately concealed
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Lack of ITT analysis
Selective reporting (reporting bias)	High risk	Lack of reporting of some of the expected outcome data
Other bias	Unclear risk	Given the described patient selection process there may be a further potential risk of bias

Pardillo 2009

Methods	Prospective, randomised, open clinical trial
Participants	47 participants (23 control, 24 intervention) with moderate croup (Taussig score between 5 to 8) aged 6 to 36 months. Excluded - patients with congenital or acquired cardiac conditions, bronchopulmonary dysplasia or stenosis or malformations of the trachea, bronchospasm at diagnosis, intolerance of oral dexamethasone or children treated with corticosteroids in the previous 2 weeks
Interventions	All patients received oral dexamethasone 0.3 mg/kg to max of 10 mg. Rescue treatment was nebulised epinephrine and oxygen via nasal route if saturation fell below 92% Control group - no treatment Intervention group - heliox 70%/30% via a mask with a reservoir to prevent re-inhalation

Pardillo 2009 (*Continued*)

	flow rate of 10 L/min for 1 hour
Outcomes	Primary outcomes: change in croup score and respiratory rate at 60 and 120 minutes Secondary outcomes: need for nebulised rescue epinephrine, admission rate, re-consultation within the following 72 hours
Notes	No information on funding source or potential conflict of interest of the authors has been provided

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Use of a computer-generated randomisation scheme
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label study; assessors knew which arms of the study participants belonged to
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no participants lost to follow-up
Selective reporting (reporting bias)	High risk	Results for the patients who required rescue epinephrine reported, but outcomes for those who were admitted or who re-presented at 72 hours were not reported
Other bias	Unclear risk	Assessors may have influenced overall outcomes due to the lack of blinding

ED: Emergency Department
ITT: intention-to-treat

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Beckmann 2000	Case report (2009 and 2013 searches)
Brown 2002	Review (from 2013 search)

(*Continued*)

Choi 2012	Review (from 2013 search)
DiCecco 2004	Case report
Duncan 1979	Case series (2009 and 2013 searches)
Frazier 2010	Review (from 2013 search)
Gupta 2005	Review
Iglesias 2007	Cohort study
Johnson 2009	Review
Kaditis 1998	Not RCT (from 2013 search)
Kline-Krammes 2012	Review (from 2013 search)
Myers 2004	Review
Myers 2006	Review (2009 and 2013 searches)
Nelson 1982	Case series
Nicolai 2012	Review (from 2013 search)
Pitluk 2011	Not RCT (from 2013 search)
Rosekrans 1998	Not RCT (from 2013 search)
Smith 1999	Case reports
Wald 2010	Not RCT (from 2013 search)
Wright 2005	Not RCT (from 2013 search)

RCT: randomised controlled trial

DATA AND ANALYSES

Comparison 1. Heliox versus oxygen 30%

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean change in croup score	1	15	Mean Difference (IV, Fixed, 95% CI)	0.83 [-0.70, 2.36]
2 Westley croup score at 20 min	1	15	Mean Difference (IV, Fixed, 95% CI)	-0.57 [-1.46, 0.32]
3 Heart rate at 20 min	1	15	Mean Difference (IV, Fixed, 95% CI)	14.5 [-8.49, 37.49]
4 Respiratory rate at 20 min	1	15	Mean Difference (IV, Fixed, 95% CI)	6.40 [-1.38, 14.18]
5 Oxygen saturation at 20 min	1	15	Mean Difference (IV, Fixed, 95% CI)	-0.40 [-1.68, 0.88]

Comparison 2. Heliox versus placebo or no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Need for rescue adrenaline	1	47	Odds Ratio (M-H, Fixed, 95% CI)	0.16 [0.02, 1.46]
2 Taussig croup score at 60 min	1	47	Mean Difference (IV, Fixed, 95% CI)	-1.12 [-2.06, -0.18]
3 Taussig croup score at 120 min	1	47	Mean Difference (IV, Fixed, 95% CI)	-0.71 [-1.72, 0.30]
4 Respiratory rate at 60 min	1	47	Mean Difference (IV, Fixed, 95% CI)	-4.94 [-9.66, -0.22]
5 Respiratory rate at 120 min	1	47	Mean Difference (IV, Fixed, 95% CI)	-3.17 [-7.83, 1.49]
6 Number of children admitted	1	47	Odds Ratio (M-H, Fixed, 95% CI)	0.46 [0.04, 5.41]
7 Number of re-presentations to ED	1	47	Odds Ratio (M-H, Fixed, 95% CI)	0.95 [0.12, 7.41]

Analysis 1.1. Comparison 1 Heliox versus oxygen 30%, Outcome 1 Mean change in croup score.

Review: Heliox for croup in children

Comparison: 1 Heliox versus oxygen 30%

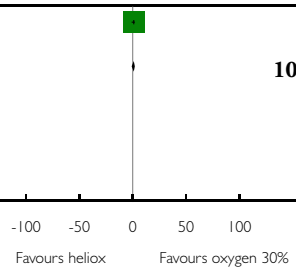
Outcome: 1 Mean change in croup score

Study or subgroup	Heliox N	Heliox Mean(SD)	Oxygen 30% N	Oxygen 30% Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Terregino 1998	8	2.25 (1.75)	7	1.42 (1.27)		100.0 %	0.83 [-0.70, 2.36]
Total (95% CI)	**8**		**7**			**100.0 %**	**0.83 [-0.70, 2.36]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.06 (P = 0.29)

Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1 Heliox versus oxygen 30%, Outcome 2 Westley croup score at 20 min.

Review: Heliox for croup in children

Comparison: 1 Heliox versus oxygen 30%

Outcome: 2 Westley croup score at 20 min

Study or subgroup	Heliox N	Mean(SD)	Oxygen 30% N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Terregino 1998	8	1 (0.76)	7	1.57 (0.97)		100.0 %	-0.57 [-1.46, 0.32]
Total (95% CI)	**8**		**7**			**100.0 %**	**-0.57 [-1.46, 0.32]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.25 (P = 0.21)

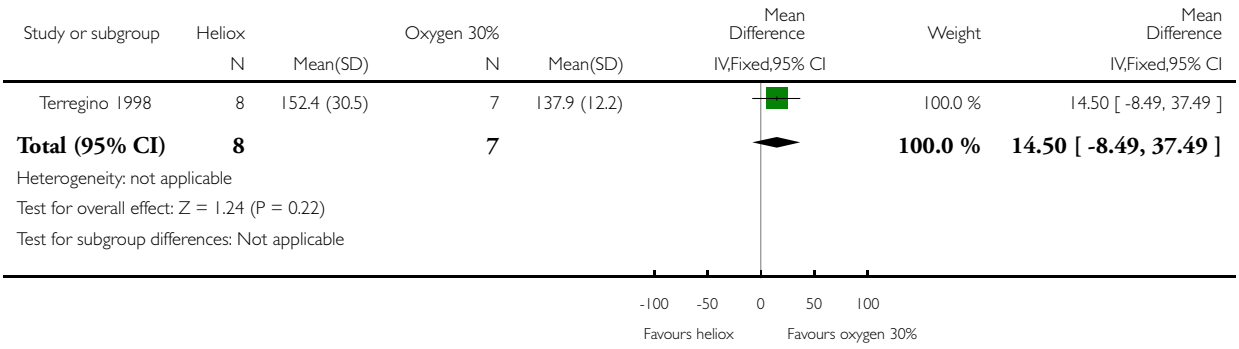
Test for subgroup differences: Not applicable

Analysis 1.3. Comparison 1 Heliox versus oxygen 30%, Outcome 3 Heart rate at 20 min.

Review: Heliox for croup in children

Comparison: 1 Heliox versus oxygen 30%

Outcome: 3 Heart rate at 20 min

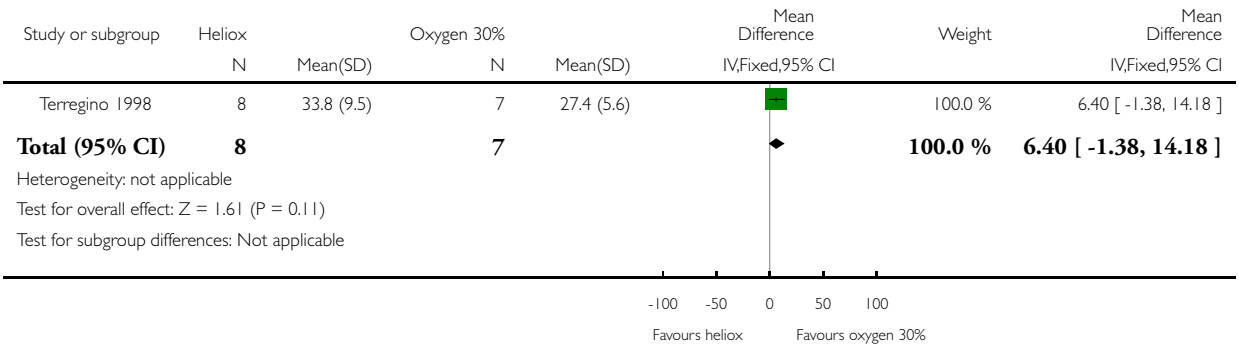


Analysis 1.4. Comparison 1 Heliox versus oxygen 30%, Outcome 4 Respiratory rate at 20 min.

Review: Heliox for croup in children

Comparison: 1 Heliox versus oxygen 30%

Outcome: 4 Respiratory rate at 20 min



Analysis 1.5. Comparison 1 Heliox versus oxygen 30%, Outcome 5 Oxygen saturation at 20 min.

Review: Heliox for croup in children

Comparison: 1 Heliox versus oxygen 30%

Outcome: 5 Oxygen saturation at 20 min

Study or subgroup	Heliox N	Mean(SD)	Oxygen 30% N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Terregino 1998	8	99 (1.5)	7	99.4 (1)		100.0 %	-0.40 [-1.68, 0.88]
Total (95% CI)	**8**		**7**			**100.0 %**	**-0.40 [-1.68, 0.88]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.61 (P = 0.54)

Test for subgroup differences: Not applicable

Analysis 2.1. Comparison 2 Heliox versus placebo or no treatment, Outcome 1 Need for rescue adrenaline.

Review: Heliox for croup in children

Comparison: 2 Heliox versus placebo or no treatment

Outcome: 1 Need for rescue adrenaline

Study or subgroup	Heliox n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Pardillo 2009	1/24	5/23		100.0 %	0.16 [0.02, 1.46]
Total (95% CI)	**24**	**23**		**100.0 %**	**0.16 [0.02, 1.46]**

Total events: 1 (Heliox), 5 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 1.63 (P = 0.10)

Test for subgroup differences: Not applicable

Analysis 2.2. Comparison 2 Heliox versus placebo or no treatment, Outcome 2 Taussig croup score at 60 min.

Review: Heliox for croup in children

Comparison: 2 Heliox versus placebo or no treatment

Outcome: 2 Taussig croup score at 60 min

Study or subgroup	Heliox N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Pardillo 2009	24	2.62 (1.69)	23	3.74 (1.6)		100.0 %	-1.12 [-2.06, -0.18]
Total (95% CI)	**24**		**23**			**100.0 %**	**-1.12 [-2.06, -0.18]**

Heterogeneity: not applicable

Test for overall effect: Z = 2.33 (P = 0.020)

Test for subgroup differences: Not applicable

Analysis 2.3. Comparison 2 Heliox versus placebo or no treatment, Outcome 3 Taussig croup score at 120 min.

Review: Heliox for croup in children

Comparison: 2 Heliox versus placebo or no treatment

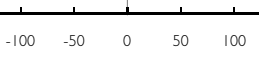
Outcome: 3 Taussig croup score at 120 min

Study or subgroup	Heliox N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Pardillo 2009	24	1.46 (1.25)	23	2.17 (2.16)		100.0 %	-0.71 [-1.72, 0.30]
Total (95% CI)	**24**		**23**			**100.0 %**	**-0.71 [-1.72, 0.30]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.37 (P = 0.17)

Test for subgroup differences: Not applicable



Analysis 2.4. Comparison 2 Heliox versus placebo or no treatment, Outcome 4 Respiratory rate at 60 min.

Review: Heliox for croup in children

Comparison: 2 Heliox versus placebo or no treatment

Outcome: 4 Respiratory rate at 60 min

Study or subgroup	Heliox N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Pardillo 2009	24	30.67 (7.2)	23	35.61 (9.15)		100.0 %	-4.94 [-9.66, -0.22]
Total (95% CI)	**24**		**23**			**100.0 %**	**-4.94 [-9.66, -0.22]**

Heterogeneity: not applicable

Test for overall effect: Z = 2.05 (P = 0.040)

Test for subgroup differences: Not applicable

Analysis 2.5. Comparison 2 Heliox versus placebo or no treatment, Outcome 5 Respiratory rate at 120 min.

Review: Heliox for croup in children

Comparison: 2 Heliox versus placebo or no treatment

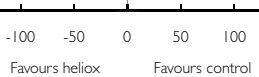
Outcome: 5 Respiratory rate at 120 min

Study or subgroup	Heliox N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Pardillo 2009	24	29 (7.82)	23	32.17 (8.44)		100.0 %	-3.17 [-7.83, 1.49]
Total (95% CI)	**24**		**23**			**100.0 %**	**-3.17 [-7.83, 1.49]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.33 (P = 0.18)

Test for subgroup differences: Not applicable

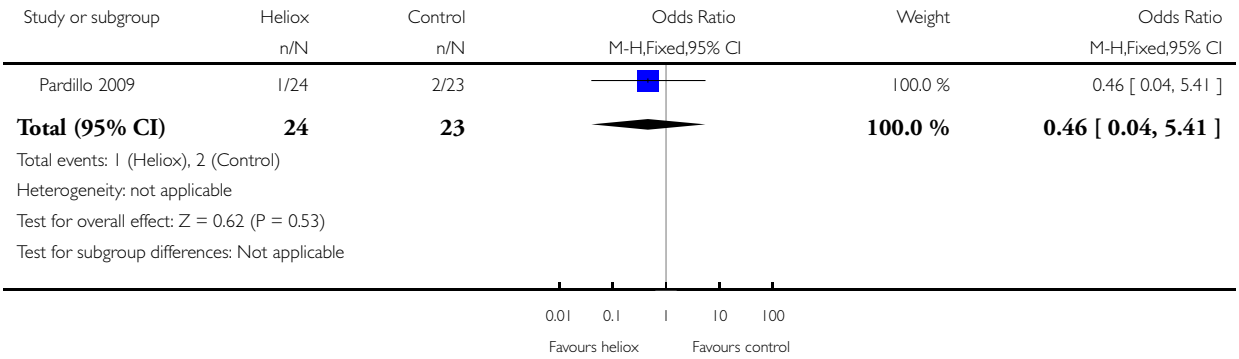


Analysis 2.6. Comparison 2 Heliox versus placebo or no treatment, Outcome 6 Number of children admitted.

Review: Heliox for croup in children

Comparison: 2 Heliox versus placebo or no treatment

Outcome: 6 Number of children admitted

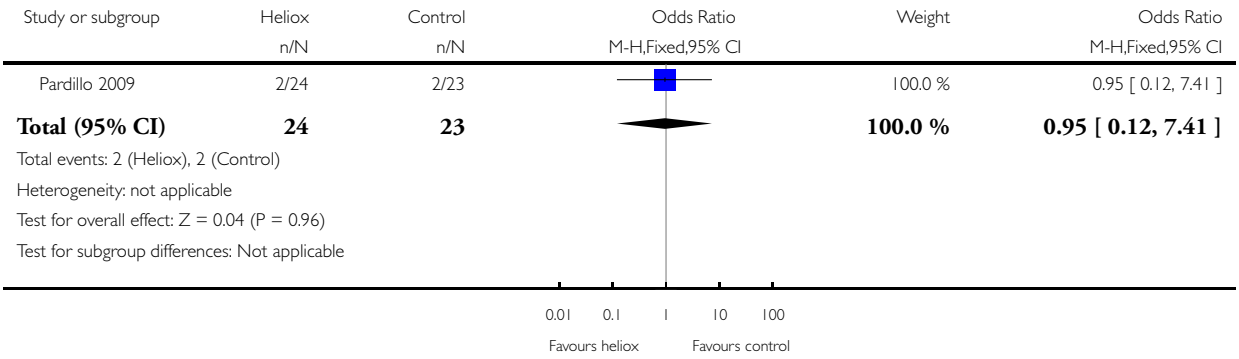


Analysis 2.7. Comparison 2 Heliox versus placebo or no treatment, Outcome 7 Number of re-presentations to ED.

Review: Heliox for croup in children

Comparison: 2 Heliox versus placebo or no treatment

Outcome: 7 Number of re-presentations to ED



ADDITIONAL TABLES

Table 1. Summary of studies table

Authors	Number of participants	Croup severity	Pre-randomisation treatment	Intervention and duration of administration	Comparison and duration of administration	Outcome time points
Terregino 1998	15	Mild	None	Humidified helium-oxygen mixture 70%/30% over 20 minutes	Humidified oxygen 30% over 20 minutes	Immediate - 20 minutes post-treatment
Weber 2001	29	Moderate to severe	Intramuscular dexamethasone 0.6 mg/kg	Helium-oxygen inhalation (70%/30%) and up to 2 normal saline nebulisers over 3 hours	Oxygen (100%) and up to 2 doses of nebulised racaemic epinephrine over 3 hours	Immediate - 30 minutes, medium - 60 and 90 minutes, long-term 120, 180 and 240 minutes
Pardillo 2009	47	Moderate	Oral dexamethasone 0.3 mg/kg	Helium-oxygen 70%/30% over 1 hour	No treatment	Immediate - no, medium - 60 minutes, long-term - 120 minutes

APPENDICES

Appendix 1. Details of previous search

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2009, Issue 2) which contains the Cochrane Acute Respiratory Infections (ARI) Group's Specialised Register; MEDLINE (1950 to June week 3 2009); EMBASE (1974 to 2009 week 25) and CINAHL (1982 to June 2009).
MEDLINE and CENTRAL were searched using the following terms. The search terms were adapted for EMBASE and CINAHL.

MEDLINE (Ovid)

1 exp Croup/
2 laryngotracheit*.mp.
3 laryngotracheo*.mp.
4 "laryngo tracheo bronchit*".mp.
5 croup.mp.
6 helium.mp.
7 heliox.mp.
8 "he-O2".mp.
9 heO2.mp.

10 “he O2”.mp.
11 exp Helium/
12 “young adult*”.mp.
13 (infant* or baby or babies or newborn* or paediatric* or pediatric* or child* or teen* or neonat* or adolescen*).mp.
14 1 or 2 or 3 or 4 or 5
15 6 or 7 or 8 or 9 or 10 or 11
16 12 or 13
17 14 and 15 and 16

EMBASE (Ovid) 1980 to Week 25 2009

1 exp Croup/
2 croup.mp.
3 laryngotracheit*.mp.
4 “laryngo tracheo bronchit*”.mp.
5 laryngotracheo*.mp.
6 exp Helium/
7 exp Heliox/
8 helium.mp.
9 heliox.mpl
10 “He-O2”.mp.
11 HeO2.mp.
12 “young adult*”.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (31526)
13 (infant* or baby or babies or newborn* or paediatric* or pediatric* or child* or teen* or neonat* or adolescen*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (1308855)
14 1 or 2 or 3 or 4 or 5
15 6 or 7 or 8 or 9 or 10 or 11
16 12 or 13
17 14 and 15 and 16

CINAHL (NHS Healthcare Databases Advanced Search) 1981 to 26 June 2009

1. CROUP/
2. laryngotracheo*.af.
3. croup.af.
4. laryngotracheit*.af.
5. “laryngo trachea bronchit*”.af.
6. HELIUM/
7. helium.af.
8. heliox.af.
9. “he-O2”.af.
10. “he O2”.af.
11. heO2.af.
12. (infant* OR baby OR babies OR newborn* OR pediatric* OR paediatric* OR child* OR teen* OR neonat* OR adolescen*).af.
13. “young adult*”.af.
14. 1 OR 2 OR 3 OR 4 OR 5
15. 6 OR 7 OR 8 OR 9 OR 10 OR 11
16. 12 OR 13
17. 14 AND 15 AND 16

Appendix 2. EMBASE (Elsevier) search strategy

#13 #7 AND #12
#12 #8 OR #9 OR #10 OR #11
#11 heo2:ab,ti OR 'he-o2':ab,ti OR 'he o2':ab,ti
#10 helium*:ab,ti OR heliox:ab,ti
#9 'heliox'/de
#8 'helium'/de
#7 #1 OR #2 OR #3 OR #4 OR #5 OR #6
#6 parainfluenza*:ab,ti
#5 'parainfluenza virus 1'/de OR 'parainfluenza virus 2'/de OR 'parainfluenza virus'/de
#4 laryngotracheo*:ab,ti OR laryngotracheit*:ab,ti OR 'laryngo tracheo bronchitis':ab,ti OR 'laryngo-tracheo-bronchitis':ab,ti
#3 'laryngotracheobronchitis'/de
#2 croup:ab,ti
#1 'croup'/de

Appendix 3. CINAHL search strategy

S11 S4 and S10 S
S10 S5 or S6 or S7 or S8 or S9
S9 TI helium N1 oxygen OR AB helium N1 oxygen
S8 TI (heo2 or "he o2" or "he-o2") OR AB (heo2 or "he o2" or "he-o2")
S7 TI heliox OR AB heliox
S6 TI helium* OR AB helium*
S5 (MH "Helium") S
S4 S1 or S2 or S3
S3 TI (laryngotracheit* or laryngotracheo* or "laryngo tracheo bronchitis" or "laryngo-tracheo-bronchitis") OR AB (laryngotracheit* or laryngotracheo* or "laryngo tracheo bronchitis" or "laryngo-tracheo-bronchitis")
S2 TI croup OR AB croup OR TI parainfluenza* OR AB parainfluenza*
S1 (MH "Croup")

Appendix 4. Web of Science (Thomson Reuters) search strategy

Topic=(croup or laryngotracheit* or laryngotracheo* or laryngotracheobronchit* or laryngo-tracheo-bronchit* or parainfluenza*) AND Topic=(helium* or heliox or heo2 or he-o2 or "he o2")
Time span = All Years. Databases = SCI-EXPANDED, CPCI-S.

Appendix 5. LILACS (BIREME) search strategy

(mh:croup OR croup OR crup OR crupe OR mh:"Parainfluenza Virus 1, Human" OR mh:"Parainfluenza Virus 2, Human" OR mh:"Parainfluenza Virus 3, Human" OR parainfluenza* OR laryngotracheobronchit* OR laryngotracheit* OR "laryngo tracheo bronchitis" OR "laryngo-tracheo-bronchitis" OR "Virus de la Laringotraqueobronquitis Aguda" OR "Virus Crup-Asociado" OR "Vírus da Laringotraqueobronquite Aguda" OR "Vírus Associado a Crupe") AND (mh:helium OR helium* OR helio OR hélio OR heliox OR heo2 OR "he o2" OR "he-o2") AND db:("LILACS")

WHAT'S NEW

Last assessed as up-to-date: 12 November 2013.

Date	Event	Description
12 November 2013	New citation required and conclusions have changed	One new included trial added to the evidence in favour of using heliox in children with moderate to severe croup
12 November 2013	New search has been performed	Searches updated. We identified one new included trial (Pardillo 2009) and excluded 10 new trials (Brown 2002; Choi 2012; Frazier 2010; Kaditis 1998; Kline-Krammes 2012; Nicolai 2012; Pitluk 2011; Rosekrans 1998; Wald 2010; Wright 2005).

HISTORY

Protocol first published: Issue 4, 2007

Review first published: Issue 2, 2010

Date	Event	Description
7 September 2012	Amended	Withdrawn.
8 July 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

This review is based on the withdrawn review by C Vorwerk and TJ Coats. The current author team updated the searches, added one new study and made considerable changes to the text.

IM led the review team and IM and NS drafted the review. MLVD provided methodological support and TM provided content expertise. All authors contributed to the draft and interpretation of the findings and approved the final version of the review.

DECLARATIONS OF INTEREST

None.

SOURCES OF SUPPORT

Internal sources

- Funding, Not specified.

None

External sources

- Funding, Not specified.

None

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

No changes were made to the methodology applied in the withdrawn review.

NOTES

The secondary outcomes in this 2013 updated review have been expanded to be consistent with other Cochrane Reviews of interventions for croup.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenal Cortex Hormones [therapeutic use]; Airway Obstruction [etiology; *therapy]; Airway Resistance [drug effects]; Bronchodilator Agents [therapeutic use]; Croup [*complications]; Dexamethasone [therapeutic use]; Epinephrine [therapeutic use]; Helium [*administration & dosage]; Oxygen [*administration & dosage]; Oxygen Inhalation Therapy [methods]; Randomized Controlled Trials as Topic

MeSH check words

Child, Preschool; Humans; Infant